

AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. §1.121 the following is a complete listing of the claims of the present application. In this set of claims, please amend the claims as follows. With the following amendments, the following listing of claims will replace all prior versions, and listings, of claims in the application:

1. (original) A crystal of ACE protein.
2. (original) A crystal according to claim 1 wherein the ACE protein is underglycosylated.
3. (original) A crystal according to claim 2 wherein the ACE protein is underglycosylated by removing one or more glycosylation sites and/or one or more partially glycosylated sites.
4. (original) A crystal according to claim 3 wherein the underglycosylated ACE protein comprises a mutation at amino acid 337 or amino acid 90,109, 155,337 and 586 of SEQ ID No 2.
5. (currently amended) A crystal according to ~~any one of the preceding claims-claim 1~~ comprising atoms arranged in a spatial relationship represented by at least a portion of the structure co- ordinates of Table A or Table B.
6. (currently amended) A crystal according to ~~any one of the preceding claims-claim 1~~ wherein the crystal belongs to the space group P2₁2₁2₁.
7. (currently amended) A crystal according to ~~any one of the preceding claims-claim 1~~ having unit cell dimensions of : a= 56. 47A, b=84.90 A,c=133. 99 A.

8. (currently amended) A crystal according to ~~any one of the preceding claims~~ claim 1 wherein the crystal is a crystal of human ACE protein.

9. (currently amended) A crystal according to ~~any one of the preceding claims~~ claim 1 wherein the crystal further comprises an entity bound to the ACE protein or a portion thereof.

10. (original) A crystal according to claim 9 wherein the entity is bound to the ACE protein or a portion thereof by contacting one or more residues of the ACE protein selected from : His384,Ala385, Lys542, Tyr551, Tyr554,Glu415 and His544.

11. (currently amended) A crystal according to claim 9 ~~or claim 10~~ wherein the entity modulates the activity of ACE.

12. (original) A crystal according to claim 11 wherein the entity is an inhibitor of ACE.

13. (original) A crystal according to claim 12 wherein the inhibitor of ACE is lisinopril or a derivative thereof.

14. (original) A crystal according to claim 13 comprising atoms arranged in a spatial relationship represented by at least a portion of the structure co-ordinates of Table B.

15. (original) A method of preparing a crystal of ACE protein comprising the steps of :

(a) culturing host cells comprising an underglycosylated ACE protein;

- (b) purifying the underglycosylated ACE protein; and
- (c) crystallising the underglycosylated ACE protein.

16. (original) A method according to claim 15 wherein the ACE protein is underglycosylated by removing one or more glycosylation sites and/or one or more partially glycosylated sites.

17. (currently amended) A method according to claim 15 ~~or claim 16~~ wherein the underglycosylated ACE protein comprises a mutation at amino acid 337 of SEQ ID No 2 or amino acids 90,109, 155,337 and 586 of SEQ ID No 2.

18. (currently amended) A method according to ~~any of claims 15 to 17~~ claim 15 wherein the ACE protein is crystallised using about 10 mM HEPES and about 0.1% PMSF with an equal volume of a reservoir solution containing about 15 % PEG 4000, about 50 mM $\text{CH}_3\text{COONa} \cdot 3\text{H}_2\text{O}$ pH 4.7 and about 10 μM $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$.

19. (currently amended) A method according to ~~any of claims 15 to 18~~ claim 15 wherein the crystal that is prepared has a structure defined by at least a portion of the structure co-ordinates of Table A.

20. (currently amended) A method according to ~~any of claims 15 to 19~~ claim 15 wherein the crystal belongs to the space group $\text{P}2_12_12_1$.

21. (currently amended) A method according to ~~any of claims 15 to 20~~ claim 15 wherein the crystal has the unit cell dimensions: $a = 56.47 \text{ \AA}$, $b = 84.90 \text{ \AA}$ and $c = 133.99 \text{ \AA}$.

22. (currently amended) A method according to ~~any of claims 15 to 21~~ claim 15 wherein the ACE protein is human ACE protein.

23. (currently amended) A method according to ~~any of claims 15 to 22~~ claim 15 wherein the ACE protein is crystallised in the presence of an entity.

24. (original) A method according to claim 23 wherein the entity is a modulator of ACE.

25. (original) A method according to claim 24 wherein the entity is an inhibitor of ACE.

26. (original) A method according to claim 25 wherein the inhibitor of ACE is lisinopril or a derivative thereof.

27. (original) A method according to claim 26 wherein the crystal that is prepared has a structure defined by at least a portion of the structure co-ordinates of Table B.

28. (currently amended) A method of screening for a modulator of ACE wherein the method comprises the use of a crystal ~~according to any of claims 1-14~~ of claim 1.

29. (original) A method according to claim 28 comprising the steps of: (a) providing at least a portion of the structure co-ordinates of Table A or Table B;

(b) employing at least a portion of the structure co-ordinates of Table A or Table B to design or select or synthesise a putative modulator of ACE;

(c) contacting the putative modulator of ACE with ACE or a mutant, variant, homologue, derivative or fragment thereof in the presence of a substrate; and

(d) screening the putative modulator of ACE in an assay for the potential to modulate ACE.

30. (original) A method according to claim 29 wherein at least a portion of the structure coordinates of Table A or Table B and/or the putative modulator of ACE and/or the substrate are provided on a machine-readable data storage medium comprising a data storage material encoded with machine readable data.

31. (currently amended) A method according to claim 29 ~~or claim 30~~ wherein the putative ACE modulator is from a library of compounds.

32. (currently amended) A method according claim 29 ~~or claim 30~~ wherein the putative ACE modulator is selected from a database.

33. (currently amended) A method according to claim 29 ~~or claim 30~~ wherein the putative ACE modulator is designed de novo.

34. (currently amended) A method according to claim 29 ~~or claim 30~~ wherein the putative ACE modulator is designed from a known ACE modulator.

35. (currently amended) A method according to claim 29 ~~or claim 30~~ wherein the design or selection of the putative ACE modulator is performed in conjunction with computer modelling.

36. (currently amended) A method according to ~~any of claims 28 to 35~~ claim 28 wherein the ACE modulator is useful in the prevention and/or treatment of an ACE related disorder.

37. (original) A method according to claim 36 wherein the ACE related disorder is hypertension.

38. (currently amended) A process comprising the steps of:

- (a) performing the method according to ~~any of claims 28 to 36~~ claim 28;
- (b) identifying one or more modulators of ACE; and
- (c) preparing a quantity of those one or more ACE modulators.

39. (currently amended) A process comprising the steps of:

- (a) performing the method according to ~~any of claims 28 to 36~~ claim 28;
- (b) identifying one or more ACE modulators; and
- (c) preparing a pharmaceutical composition comprising those one or more identified ACE modulators.

40. (currently amended) A process comprising the steps of:

- (a) performing the method according to ~~any of claims 28 to 36~~ claim 28;
- (b) identifying one or more ACE modulators;
- (c) modifying those one or more ACE modulators; and
- (d) optionally preparing a pharmaceutical composition comprising those one or more ACE modulators.

41. (original) A method of obtaining structural information about a molecule or a molecular complex of unknown structure by using at least a portion of the structure co-ordinates of ACE, comprising the steps of:

- (a) generating X-ray diffraction data from a crystallised molecule or molecular complex;

(b) applying at least a portion of the structure co-ordinates of ACE to said X-ray diffraction pattern to generate a three dimensional electron density map of at least a portion of the molecule or molecular complex; and

(c) using all or a portion of the structure co-ordinates of ACE to generate homology models of ACE.

42. (currently amended) An ACE modulator identified by the method of ~~any one of claims 28 to 36~~ claim 28.

43. (original) An ACE modulator according to claim 42 wherein the ACE modulator inhibits ACE.

44. (currently amended) A pharmaceutical composition comprising an ACE modulator according to claim 42 ~~or claim 43~~ and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant or any combination thereof.

45. (currently amended) A method of preventing and/or treating an ~~an~~ ACE related disorder comprising administering a modulator of ACE according to claim 42 ~~or claim 43 and/or a pharmaceutical according to claim 44~~ wherein said modulator of ACE ~~or said pharmaceutical~~ is capable of causing a beneficial preventative and/or therapeutic effect.

46. (original) A computer for producing a three-dimensional representation of ACE wherein said computer comprises:

(a) a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises the structure co-ordinates of ACE;

(b) a working memory for storing instructions for processing said computer-readable data;

(c) a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-machine readable data into said three-dimensional representation; and

(d) a display coupled to said central-processing unit for displaying said threedimensional representation.

47. (original) A machine-readable data storage medium comprising a data storage material encoded with machine readable data, wherein the data is defined by at least a portion of the structure co-ordinates of ACE in Table A or Table B.

48. (canceled)

49. (canceled)

50. (canceled)

51. (currently amended) A method of using ~~Use of~~ at least a portion of the structure co-ordinates of Table A or Table B to solve the structure of the crystalline form of any other protein with significant amino acid sequence homology to any functional domain of ACE.

52. (canceled)

53. (currently amended) ~~Use of at least a portion of the structure co-ordinates of Table A or Table B in the development of compounds that~~ The modulator of claim 43, wherein said modulator is a compound that can isomerise to reaction intermediates in the chemical reaction of a substrate or other compound that binds to ACE.

54. (currently amended) ~~Use of at least a portion of the structure coordinates of Table A or Table B to screen~~ The method of claim 28 wherein said modulator is identified from the screening of small molecule databases for chemical entities or compounds that modulate ACE.

55. (canceled)

56. (canceled)

57. (currently amended) An expression vector designated as pLEN-tACEΔ36g (1,2,3,4).

58. (currently amended) An expression vector designated as pLEN-tACEΔ36g (1,3).

59. (new) A method of screening for a modulator of ACE wherein the method comprises the use of a crystal prepared according to the method of claim 15.

60. (new) A method of preventing and/or treating an ACE-related disorder comprising administering a pharmaceutical composition according to claim 44 wherein said pharmaceutical composition is capable of causing a beneficial preventative and/or therapeutic effect.